Fifty Years of Clinical Research in *The Journal of Investigative Dermatology*

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When asked to write a paper for the 50th anniversary issue of the JID, two feelings immediately come to mind: to be very proud and honored, but, on the other hand, quite depressed because of the unexpected amount of work this task calls for. When this paper happens to bear the title ''Clinical research in the JID,'' the extent of depression starts rising exponentially with the broadness of the field as well as its lack of definition. As an antidepressant procedure, the first question to consider is then, what is clinical research?

CLINICAL RESEARCH

When asked this question what is clinical research, many people would agree that it is difficult to define. This common feeling reflects the fear of investigators, nowadays struggling for grants, to embark in laborious clinical studies on humans with a low chance of significant yield. Mouse strains and cultures of established cell lines are by far more easy to handle and to render homogenous than a group of patients. If hard to define, what do we expect from clinical research? It should provide clinicians with facts and concepts readily usable for diagnosing, understanding, and treating human diseases.

Recently, an interesting distribution of responsibility took place on the Editorial board of the JID when section associate editors were appointed. When considering the sections one may feel that clinical research is what is *not* photobiology, cell biology, immunology, pharmacology, carcinogenesis, biochemistry, biologic structure and function, extra cellular matrix, or melanocyte biology.

Does this mean that clinical research has not had an important place in this journal? In fact, out of 203 papers submitted during the last few months, 19 were considered by the Chief Editor to fall into this category, i.e., 9.3%, which represents a sizeable amount of papers.

The way of collecting data for this review was based on a remarkable subjective method. The bound volumes of the JID, starting with No 1, 1938 and ending with No 88, 1986, were looked over. The title and abstract of each article were read, and if the paper was considered of potential interest as a ''clinical research paper,'' it was quoted. An attempt was made to scan no more than 5 years per week when the JID comprised only one volume per year and five volumes when the Journal increased to two volumes per year.

Criteria for selecting an original paper, thus excluding review papers, were severalfold. One common criterion was that the message either still remains valid today or raised a controversy when it was written that suggested further studies. Other criteria were as follows: (1) first report on a new treatment, (2) particular studies done on humans, (3) first description of a technique on humans that allowed measurements of a function of the skin, (4) new clinical concepts or ''new'' diseases, or (5) studies on the pathogenesis of skin diseases. This, by no means, implies that papers not falling into these categories have no clinical impact. It is in fact my feeling that, say, the study of ''Epidermal growth in Bottlenose Dolphin (JID 85:60–63, 1985) may ultimately prove to bring important insight to the clinician dealing with a psoriatic patient. Moreover, many papers of direct potential importance for the clinician could not be included because they clearly pertain to pharmacology, immunology, genetics, etc. These topics are covered in other sections of this anniversary issue. Finally, due to my personal interest in this field, most if not all the papers dealing with vitamin A and retinoids were quoted.

All this resulted in the ''selection'' of 190 papers, some of which will be discussed in the following sections. Finally, the subjective nature of this method of selection was compared to the list of the 200 top cited articles published in this issue.

Apologies Many important reports dealing with clinical research have evidently been missed. It is hoped that the authors of these papers will understand.

Table I shows the number of papers selected through this subjective process. Twenty-one percent were subsequently found to be among the 200 top cited JID papers in the ISI report. If the papers dealing with retinoids are not included, the percentage raises to 26%. Because it is generally accepted that the citation index rate does not necessarily correlate with the ''clinical usefulness'' of a given paper, it was thought that the subjective process of selection might have some significance.

SIGNIFICANT (FIRST) PAPERS ON THERAPY (TABLE II)

''During the past few years a new group of so called antihistaminic agents has been developed and studied in Europe and in the United States,'' wrote R. Baer and M.B. Sulzberger in 1946 as the first sentence of a paper on the use of pyribenzamine [1] (Table II). Because they did not quote any other previous paper, this might have been the first on the use of systemic antihistaminics in dermatology. They treated 56 patients and found pyribenzamine to be of ''therapeutical value'' in about one half of chronic urticaria, without effect in atopic dermatitis, and sometimes of value in some cases of ''essential pruritus.'' The natural outgrowth of systemic antihistamines was the use of topical preparations. A paper on this topic was published the following year (1947) by D.J. Perry [2]. He observed that ''local application of 2% Benadryl ointment is not followed by sufficient absorption (if any) to decrease the experimentally produced histamine wheals.'' He then treated 22 patients with various pruritic dermatoses; moderate relief of itching was obtained in six and excellent relief in two. In 50% of these responders, the ointment base alone was as active as the drug. The only explanation considered for this was a lack of penetration. Dermatologists have since learned that when a drug is found to be active systemically, the topical route is frequently disappointing for many reasons other than just absorption. It is interesting that a number of topical antihistamines are still marketed and sold. The story of topical antibiotics [3,4] was more successful. Because penicillin was said to be unstable and induced frequent sensitization (M.B. Sulzberger, Ref 3) new compounds that would only be used topically and proved not to be sensitizing were searched for. Gramicidin was one of these agents, first reported by Anderson in 1947 [3], and bacitracin was used in the treatment of 155 patients by

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Table I.

Subject Section	Clinical Research Papers Selected for This Review[a]	Number and (%) of These in the 200 Cited Top
Therapy	33	4 (12%)
Peculiar experiments in humans	13	4 (30%)
New techniques	20	13 (65%)
New clinical concepts or new diseases	22	4 (18%)
Pathophysiology of some skin diseases	40	8 (20%)
Total	128	33 (26%)
Rtetinoids[b]	61	3 (5%)

[a]Selected by a subjective method (see text). Not all are commented upon in this review.
[b]Almost all papers are quoted, including papers not strictly on clinical research.

Table II. Significant Papers on Therapy

		Reference
1.	Antihistaminics. Systemic	1
2.	Antihistaminics. Topical	2
3.	Topical antibiotics	3,4
4.	HCH in the treatment of scabies	5
5.	Gelatin for fragile nails	6
6.	Study on 54 topical antipruritic agents	7
7.	Penicillin for acrodermatitis chronica antrophicans	8
8.	Systemic ACTH and cortisone treatment	9,10
9.	Topical hydrocortisone	11[a]
10.	Antimalarial treatment of lupus erythematosus and light sensitive eruptions	12–15
11.	Systemic antibiotic therapy for acne vulgaris	16
12.	Sulfones for dermatitis herpetiformis	17
13.	Benzophenones as sunscreens	18
14.	Intralesional triamcinolone	19
15.	Increased absorption of griseofulvin by fat meal	20[a]
16.	Laser used on skin	21
17.	Amount of topical preparation required for total and partial body inunction	22
18.	Controlled study of the charming of warts	24
19.	Topical 5-fluorouracile for basal cell carcinomas	25,26
20.	Beta carotene does not prvent sunburn	27
21.	Multicenter US PUVA therapy study in psoriasis	28[a]
22.	Association of oral retinoids with PUVA	29[a]
23.	Topical Capsaicin	30
24.	Naloxone has antipruritic effect	31
25.	What about azelaic acid?	32,33

[a]Quoted in the 200 top cited papers of the JID.

Miller *et al* in 1948 [4]. Reading the discussion that follows Anderson's paper is fascinating. F.D. Wiedman proposed (p. 32) ''we should remember that we may do better than confine ourselves to the extracts of these microorganisms (Gramicidin was extracted from a bacteria); we can employ the organisms themselves in the living state.'' In some ways this was conceptually the root of the concept of bacterial interference (suppression of bacterial growth by other bacteria), which unfortunately has had little impact on dermatology. Sensitization was a concern, but the acceptable rates were quite different from those considered nowadays. Miller [4] found 1% of the cases developing contact dermatitis to be ''a low sensitizing potential.''

Wooldridge [5] reported on what seems to be the first use of the gamma isomer of hexachlorocyclohexane, the popular Lindane in the treatment of scabies. He treated 72 patients with a 1% vanishing cream applied once every 24 h. He found that 95% of the patients were cured and noted ''it is doubtful if the rate of five percent relapses could be significantly lowered, no matter how intelligent and cooperant a group of patients might be.'' He also stated that ''There are as yet no reported instances of toxic symptoms in man…'' Forty years later, the patients are supposed to be as intelligent and cooperant, the drug is widely used, and the toxicity is still a matter of debate. At that time, the JID was accepting case reports. Tyson [6] found that a patient given gelatin internally ''in the hope of relieving her muscular weakness'' had her ''fragile'' nails returned to normal. He then ''treated'' twelve additional subjects (11 women, 1 man) with 7 g of commercial gelatin once a day for up to 3 months; there were 10 success. Some still use gelatin for brittle nails, but little insight on how it could bring improvement has been provided since this report.

Melton and Shelley [7] studied the effect of 54 topical preparations on the inhibition of histamme induced pruritus. Looking at the list of the compounds used in 1950, one may appreciate that very little progress has been made since. Interestingly, none of the compounds had a significant effect. Although the authors conclude that their study provided ''no experimental evidence to indicate usefulness of local antipruritic medicaments when applied to skin of normal permeability,'' many are still sold today, including Menthol, Calamine lotion, antihistamines, and topical anesthetics. It would be interesting to know what Professor Shelley is using nowadays.

In a paper entitled ''The effects of penicillin on certain hitherto incurable dermatoses'' V.H. Witten [8] confirmed the previous observations of European investigators, including N. Thyresson, that acrodermatitis atrophicans chronica improved with penicillin therapy, but noted that established atrophy was not improved. He quoted a personal discussion with his chairman, Professor M.B. Sulzberger: ''While by no means this was conclusive evidence, it once more directs attention to the possibility of treponemes playing some part in the pathogenesis.'' We know 40 years later that the ''treponemes'' were spirochetes of the genus Borellia.

M.B. Sulzberger [9] reported on the effect of ACTH, known as Armour at the time, in 44 patients with 19 different dermatologic conditions, and likewise studied various physiologic functions of the skin before, during, and after administration of ACTH. There is not a single message in Sulzberger's long paper that well reflects the excitment of dermatologists dealing with a potent systemic anti-inflammatory drug for the first time. In the same year Brunner *et al* [10] reviewed the cutaneous side-effects of ACTH and cortisone therapy, and one of the interesting conclusions was that their observations confirmed the ''causative importance of steroid hormones endogenously produced in acne vulgaris and… seborrheic dermatitis.'' ''It has been the experience of most investigators that the topical use of cortisone acetate ointment is without value in the treatment of diseases of the skin,'' said M.B. Sulzberger [11] in the first sentence of a short report on the use of ''compound F'' (17 hydroxycorticosterone 21 acetate). He treated 19 patients and observed slight improvement in seven, mostly atopic dermatitis, whereas DLE, pemphigus vulgaris, and alopecia, of course, did not respond. It seems this is the first observation on the clinical efficacy of topical steroids; it was published

in the section ''preliminary and short reports'' but is still among the 200 top cited papers of the Journal (Fig 1).

Although the first mention that Mepacrine might be of benefit in lupus erythematosus was reported in 1941 by Popoff *et al* (cited in Ref 14) and subsequently confirmed by Page in the Lancet in 1951 (cited in Ref 14), three papers [12–14] appeared in the December 1952 issue of the JID. At that time, one could start a paper by stating, like Cramer and Lewis [12], that ''no remedy for the treatment of chronic DLE has proved invariably helpful.''

''New and superior therapy for LE appear periodically in the dermatologic literature; they are then evaluated with hopeful scepticism by the profession,'' said Sawicky *et al* in Ref 13. However, of the 48 patients in the three studies, there were only six failures. Thirty-five years later there is no longer skepticism! Knox *et al* [15] later reported on the improvement by Mepacrine of cases of prurigo aestivalis and other light sensitive eruptions. He took advantage of this to propose that the drug might act in both LE and other light sensitive eruptions via a light screening effect rather than an antiplasrnodial or infectious mechanism.

PRELIMINARY AND SHORT REPORTS

HE EFFECT OF TOPICALLY APPLIED COMPOUND F IN SELECTE DERMATOSES

MARION B. SULZBERGER, M.D. AND VICTOR H. WITTEN, M.D.

It has been the experience of most investigators, with a few exceptions, that the topic of cortisone acetate ointment is without value in the treatment of diseases of the ski

TABLE I

mparison Between Areas Treated with Compound F Ointment and Those Treated wi Control Ointment

CASE	AGE	SEX	DIAGNOSIS	COMPOUND F TREATED AREAS AS COMPARED TO CONTROL SITE		
				Much better	Slightly better	No better
. (S. M.)	2	M	Atopic dermatitis		X	
. (H. W.)	16	M	Atopic dermatitis		X	
. (M. S.)	28	M	Atopic dermatitis		X	
. (H. S.)	48	F	Atopic dermatitis			X
. (C. W.)	35	F	Atopic dermatitis		X	
. (G. H.)	19	F	Atopic dermatitis		X	
. (E. M.)	35	F	Atopic dermatitis (?)	X		
. (J. L.)	18	M	Atopic dermatitis (?)			X
. (N. J.)	15	F	Psoriasis			X
. (I. M.)	50	M	Psoriasis			X
. (W. S.)	52	F	Chronic discoid lupus erythematosus			X
. (M. F.)	36	F	Chronic discoid lupus erythematosus			No control No improvement (
. (L. G.)	56	F	Chronic discoid lupus erythematosus			No control No improvement
. (J. F.)	30	F	Chronic discoid lupus erythematosus			No control No improvement
. (W. H.)	46	F	Widespread discoid or subacute lupus erythematosus		X	
. (A. K.)	34	M	Exudative discoid and lichenoid chronic dermatosis			X
. (E. S.)	41	M	Pemphigus vulgaris			No control No improvement
. (C. L.)	20	F	Alopecia areata			No control No improvement
. (W. K.)	46	M	Alopecia areata			No control No improvement

hen compound F (17-hydroxycorticosterone-21-acetate) was made available to us*, v d an ointment prepared containing the crystalline material in a concentration of 25 m

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* We are indebted to the medical division of Merck & Co., Inc., Rahway, New Jers r supplying the crystalline hydrocortisone acetate.

Figure 1. This report by Sulzberger and Witten (J Invest Dermatol 19:101–102, 1952) was a harbinger of great things to come, the effect of potent topical steroids on the practice of dermatology. It is number 106 of the 200 most cited papers in the JID.

''The lesions of acne have often been found to harbor corynebacterium acnes… it was felt that if the corynebacterium does contribute to the pathogenesis of acne vulgaris, then erythromycin might be of definite benefit'' stated Van de Erve in 1954 [16]. He treated 60 cases of acne vulgaris and observed excellent control of pustules but no effect on the ''sebaceous secretion.'' Because the author did not quote any previous report, it seems that, unless the reviewers and editors did not do their job, this might be the first report on the therapy of acne with systemic antibiotic.

Sometimes the JID may have served as a tool to disseminate concepts that were not accepted even if previously published in the Archives of Dermatology. Cornblett complained [17] that ''not withstanding good results shown in his previous study on five patients'' treated with Dapsone for dermatitis herpetiformis, ''this form of therapy did not become popular.'' He reported on 14 more patients. His paper is written like an editorial or a comment rather than a scientific paper. Despite its historical significance this might explain why it is not quoted in the 200 top cited papers of the JID.

In 1957, a new group of ultraviolet light absorbers, benzophenones, was presented [18] and compared to previously used sunscreening agents such as PABA and tannic acid. The paper, as many at that time, is followed by a discussion in which the author was asked by Dr Kestin and Dr Baer about the safety and allergenic potential of benzophenones. The author prudently answered ''time alone will tell the clinical application of the benzophenones.'' Time told us, it's O.K.

''The physician who necessarily regards the disappearance of a lesion as certain evidence of cure would indeed be naive. However, *the patient* whose skin lesion has for months resisted the expert therapy of dermatologist is certainly impressed if, after a single injection, the lesion disappears within a few days'' [19]. There were 90 patients in this trial and the injection was a sterile aqueous solution of triamcinolone acetonide that was recently made available for investigative use. This historical paper on intralesional steroid therapy reflects the excitement not only of the patients but also the author, who wrote that he felt the data ''should be reported immediately!''

In 1961 griseofulvin was the only systemic antimycotic drug to be used for dermatophytic infections, and many cases were found unresponsive. In a well-designed study, R.G. Crounse [20] found that a high fat meal nearly doubled the blood levels of griseofulvin following a test dose. In order to avoid the patients needing this drug putting on weight, the industry has now provided us with new formulations that render this important finding less applicable.

The first paper on laser use on human skin appears to be by Goldman *et al* in 1963 [21]. They used a ruby laser with an output of more than 5 joules, and their observations were not dramatic.

How many grams of topical preparation are needed for total body inunction? Many more when a ''superficially instructed individual'' does it, as compared to a ''trained operator'' with a range from 7.7 to 114.8 g [22]. This important and clinically relevant study has probably received little attention because it is not in the 200 top cited papers, but it contains pertinent observations that seem to be still usable today, especially for nurses.

In his book *The Medusa and the Snail* [23] Lewis Thomas wrote ''Warts are wonderful structures… They can be made to go away by something that can only be called thinking, or something like thinking.'' He probably did not read the JID paper on ''the charming of warts'' [24]. This was a controlled study using two procedures: a slight electric shock or a simulated x-ray exposure. The conclusion was that the suggestion, or charming, does not succeed when experimentally controlled.

What appear to be the first controlled double-blind studies on the effect of topical 5-fluorouracil on basal cell carcinomas were published in 1965 [25,26]. Topical 5-fluorouracil proved to be superior to other topically applied anti-tumor agents such as

Actinomycin D, Nitrogen mustard, Methotrexate, and 5-Mercaptouracile. We later learned that basal cell carcinomas are best treated by excision or radiotherapy, but 5-fluorouracil is still widely used for actinic keratosis.

Important studies from the Boston group often first appeared in the *New England Journal of Medicine,* but further analyses were usually published in the JID. Because they had recently found that feeding beta-carotene ameliorates the photosensitivity of patients with erythropoietic protoporphyria, the same group of investigators wanted to know whether beta-carotene could serve as a photoprotective agent for sunburn [27]. The answer was no, and we still await for a systemic sun protective agent.

The multicenter trial on PUVA of Melski *et al* [28] appeared in the JID in 1977, three years after the first report in the *New England Journal of Medicine*. This is a key paper on 1308 U.S. patients, which is third on the list of the 200 top cited papers in the JID.

That PUVA might be potentiated by oral retinoids was first demonstrated by Fritsch *et al* [29]. Although this was not a double blind study, it drastically modified the use of both retinoids and PUVA in the treatment of psoriatic patients.

Although the drug is only used, so far, for zoster pain, Capsaicin might have a brighter future. Bernstein *et al* [30] reported in 1981 that topical application of this pugent principle of hot pepper did inhibit histamine-induced axon-reflex vasodilatation, possibly by depleting substance P from local sensory nerve terminals. Also in the line of ''neurodermatology'' is the report by the same author [31] that Naloxone, an opiate antagonist, has an antipruritic effect. So far this important observation has no therapeutical application because the opiate antagonists are not easy to use in practice.

This section on ''significant papers on therapy'' will be closed not by refering to a paper but rather to a letter to the editor and its reply [32,33]. Both are on azelaic acid and its effect as a depigmenting and chemotherapeutic agent. For the reader who is not an expert in the field, the Letter to the Editor is sometimes as informative as the original papers, because the controversy is not dampened by the review process!

PECULIAR EXPERIMENTS IN HUMANS

It is interesting that the first study selected on the experimental induction of photoallergy to sulfanilamide [34] was done on volunteers ''including myself'' wrote the author. Not all the studies in humans, subsequently reported, included such an ''ethical control.'' The paper by W.B. Shelley and Horwath on experimental miliaria in humans [35] is one of the many studies dealing with sweat disorders that were published in the JID during and just after WWII. The interest in this topic was most probably due to exposure of U.S. soldiers to tropical climates.

The other studies selected for this section fall into three categories (1) the induction of either sensitization, flare, or tolerance to simple chemicals, (2) the reproduction of superficial bacterial or fungal infections, and (3) the exposure of human skin to newly purified mediators of inflammation.

Sensitization to Simple Chemicals In the study by Sidi [36] patients with topical sensitization to sulfonamides or anesthetics were exposed to ''oral or injected challenge'' to both drugs in order to demonstrate *systemic* cross reactivity amongst the ''para group.'' They concluded that *''cutaneous* sensitization can bring about *systemic* sensitization and occasionally serious accidents, which can be caused by the agent that has sensitized the patient as well as by an entire group of chemically related substances.''

Passive transfer of contact hypersensitivity in humans had been unsuccessfully tried several times with the use of blister fluid or white blood cell suspension, etc. In 1957 Epstein and Kligman [37] used concentrated leucocytes obtained from venous blood of sensitized donors. They were able to transfer sensitization to three contact allergens in males aged 20–45 years, and to one contact allergen in one out of six children.

R. Baer was a pioneer in contact sensitivity. When nitrogen mustard was found to be topically effective in some cases of psoriasis, it became evident that it was also a potent contact allergen. Because the drug ''fulfilled the requirement for a trial of prevention of allergic contact sensitization in man'' (i.e., had been used intravenously for many years), the trial was performed [38]. Unfortunately, it was a failure, which was interpreted as being possibly due to the schedule used. Subsequent studies did not establish a proper tolerogenic schedule that would prevent sensitization in all patients. This well demonstrates how difficult relevant clinical research is in humans.

Experimental Infections of Human Skin An impressive study, in many respects, was that of Vilanova *et al* [39], who infected human nails with fungi such as *T. schoenleini,* rosaceum, rubrum, etc. Fortunately the success in inducing onychomycosis was only 24%, and this persisted for 6 months at most. More recently [40], 27 psoriatic patients were inoculated on psoriatic plaques with either Trichophyton rubrum or Mentagrophytes; 16 developed infection with a better score for Trichophyton rubrum. This study demonstrated that psoriatic scales are not repellent for these two fungi as previously thought, and that a psoriatic patient, especially when under occlusive topical steroid therapy, may develop tinea ''incognita.'' Tinea versicolor was experimentally reproduced in humans [41,42]. The paper by Burke [41] is among the 200 top cited papers in the JID, probably because it provided not only evidence for experimental infection, which was achieved in several instances, but also because it related it to underlying systemic disease such as Cushing's syndrome, systemic steroid therapy, etc. It still stands as one of the key references in the field.

Bacteria were also inoculated to human skin, but it was not easily infected. Duncan *et al* [43] had to (i) apply Staphyloccoci and Streptococci in the form of an overnight broth culture, (ii) stab through the drop of inoculate with a blood lancet, and (iii) cover the site with non-porous plastic tape. The highest rate of successful infection was 38% on the legs and only 13% on the arms. Inoculation on normal skin produced only one infection in 78 inoculations. More recently, Leyden *et al* [44] confirmed and extended these observations and wrote ''we have demonstrated for the first time that localized self healing infections can be regularly produced with several strains of streptococci.'' Normal intact skin was never colonized or infected, whereas inoculation on skm damaged by superficial scarification resulted in localized infections when the wound was covered by an impermeable plastic film. Nice color photographs illustrate the clinical evolution of the lesions in this paper. They should be used when teaching on impetigo!

Mediators of Inflammation When a mediator of inflammation becomes available in sufficiently purified form, the natural tendency of the experimental dermatologist is to either apply it topically or inject it intradermally in human skin. There were numerous studies on histamine that, for lack of space, will not be commented upon here. Rather, two studies on leukotriene B4 were selected because they well illustrate the importance of the route of administration. Soter *et al* [45] injected leukotriene B4 and noted erythema and wheal formation with dermal infiltrate of neutrophils on histology. When Camp *et al* [46] applied leukotriene B4 topically, they induced intra-epidermal neutrophilic abcesses. Unfortunately, they did not induce psoriatic changes (Fig 2).

NEW TECHNIQUES FOR USE ON HUMAN SKIN WITH SIGNIFICANT IMPACT ON EXPERIMENTAL DERMATOLOGY AND DIAGNOSIS OF SKIN DISEASES

This is probably the section that groups the major contributions of investigative dermatology to clinical practice. Interestingly, 65% of the

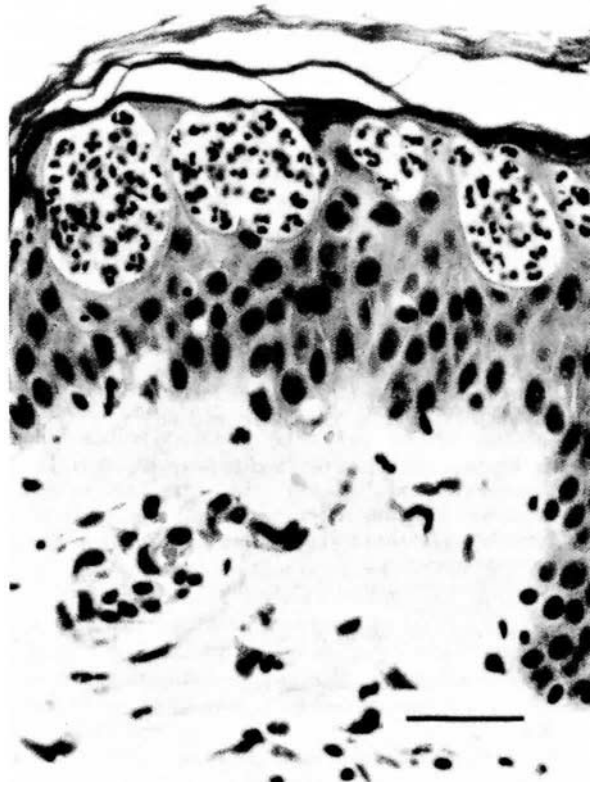


Figure 2. Topical application of leukotriene B_4 produces intraepidermal abcesses in normal skin, but not the full clinical and histologic picture of psoriasis. (From Camp R *et al*: J Invest Dermatol 82:202–204, 1984)

papers selected for this section are in the list of the 200 top cited papers in the JID. Most of these papers are commented on in other articles in this issue; however, it seemed relevant to list them as a perspective (Table III).

This list includes Pinkus' historical papers [47,48] on the strip method of removing horny layers. The story starts [47] with an illuminating sentence: ''It occurred to me that Wolf's method might be valuable in many other ways—(than just recovering stratum corneum for examination)—for gaining information not only about the horny layer but about the entire epidermis.'' It ends [48] with another key comment: ''Loss of keratinized cells is believed to be the primary stimulus of epidermal proliferation.''

The paper by Van Scott *et al* [49] describes in detail the method for examining hair roots, later called trichogramm. As a first application it establishes that the hair fall out induced by a high dose of methotrexate therapy is anagen effluvium.

Two key papers on the biology of sebaceous glands and the way of measuring sebum excretion, one by Kligman and Shelly [50], the other by Strauss and Pocchi [51], are in the 200 top cited papers in the JID. It seems fair to include with these the paper published 10 years earlier by Jones *et al* [52], because it appears to have paved the way for the latter studies.

In 1963 Burnham *et al* [53] made the first report on the use of the direct immunofluorescent (so written) method in skin lesions of lupus erythematosus, ''eczema solare,'' psoriasis, seborrheic dermatitis and mycosis fungoides. The ''lupus band'' was detected in the nine patients with LE, six systemic and three chronic. This was not the first attempt to detect immunoreactants in skin lesions with this method. Burnham *et al* even quote two previous studies published 1 year before in the *Archives of Dermatology,* where, unfortunately for the investigators, lupus erythematosus was not analyzed.

Table III. New Techniques for Experimentation and Diagnosis

		Reference
1.	Examination of the epidermis by the strip method	47[a],48[a]
2.	Method for examining hair roots (trichogramme)	49[a]
3.	Measuring sebum excretion and its significance	50[a],51[a],52
4.	Lupus band test. (Direct immunofluorescence on lesional skin)	53[a]
5.	Autoradiographic analysis of turn over in psoriasis	54[a]
6.	Suction blister method	55,56[a],57[a]
7.	IgA deposits in dermatitis herpetiformis	58[a]
8.	Fixative solution for the transport of specimens for immunofluorescence	59[a]
9.	Sodium chloride. Separated skin for indirect immunofluorescence	60
10.	Immunoelectron microscopy of bullous pemphigoid	61,62[a]
11.	Identification of T and B cells by the rosette method	63[a]
12.	Monoclonal antibodies for immunohistochemistry and Western Blots[b]	64,65
13.	Western Blot analysis of skin extract (cited on this page)	
14.	Measurement of cutaneous blood flow	66,67

[a]Quoted in the 200 top cited papers in the JID.
[b]Examples.

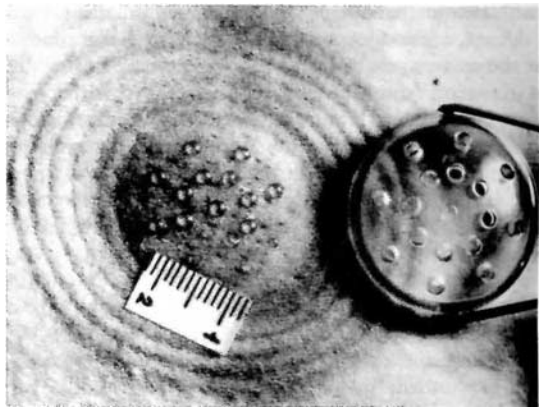


Figure 3. Proper demonstration of the suction blister technique by Kiistala (J Invest Dermatol 50:129–137, 1968).

The paper by Weinstein and Van Scott [54] on the autoradiographic analysis of turnover time after dermal injection of tritiated thymidine provided direct information on the kinetics of psoriatic epidermis as compared to normal. It established that turnover time in psoriasis was about 2 d versus 13 in normal.

The suction blister method is now widely used in investigative dermatology. What seems to be the first report on this phenomenon appeared in the JID in 1950 [55], but the method was properly described by Kiistala and Mustakallio in the JID (Fig 3) in 1967 and 1968 [56,57], three years after their first paper in the Lancet (cited in Ref 57).

Many significant papers on immunofluorescence appeared from the late 1960s to the early 1980s. Three have been selected for this review: (i) the report by Chorzelski *et al* [58] establishing the direct immunofluorescent pattern of dermatitis herpetiformis and adding a further strong criterion for its distinction from bullous pemphigoid; (ii) the description by Michel *et al* [59] of a solution that provides

adequate preservation of tissue fixed immunoglobulins in skin biopsies (this allowed broadening the use of direct immunofluorescence to private offices); and (iii) a much more recent paper by Gammon *et al* [60] on indirect immunofluorescence on 1.0 M sodium chloride-separated skin (this technique allows differentiating anti-lamina lucida and anti-sublamina densa antibodies without the use of electron microscopy, i.e., bullous pemphigoid from epidermolysis bullosa acquisita). This paper well illustrates how basic research on the biology of the dermo-epidermal junction might ultimately yield a simple yet useful diagnostic test.

Next, the period of immunoelectron microscopy and that of new tools for characterizing cell subpopulations in the skin. Two important papers on immunoelectron microscopy of bullous pemphigoid were published in 1975, both demonstrating the localization of the IgG deposits within the lamina lucida [61,62]. The era of identifying cell subsets in the skin started with the use of the rosette technique [63]. The conclusion of the paper was ''it is therefore possible to distinguish between B cells, T cells and histiocytes in skin lesions.'' This seems so evident now that one has to remember the difficulties of playing with the rosette technique on histologic slides *in vitro*. Then came the monoclonal antibodies and all the journals were loaded with papers on their use. Identifying cell subsets became possible not only within lymphomonocytic infiltrates but also within epithelial populations. These tools are now indispensable for the proper identification of many skin lesions and tumors. The paper by Moll and Moll [64] illustrates, as an example, what these new technical tools do bring to clinical research. By using both immunohistochemistry and Western Blot techniques they analyzed the cytoskeleton of extramammary Paget's disease and showed that the keratin pattern of Paget's cells is identical to that of the secretory, but not the ductal, cells of both apocrine and eccrine glands. Another example is the use of monoclonal antibody in the prenatal diagnosis of dystrophic epidermolysis bullosa, as recently shown by Eady *et al* [65].

The importance of Western Blot analysis in clinical dermatology is just being appreciated; the reader will find more details in the paper by Krueger and Stingl in this issue.

Although the author of this review is not familiar with these techniques, measurement of cutaneous blood flow seems to have an important future. What appears to be the first paper on the use of laser doppler for the measurement of cutaneous blood flow was published in 1977 [66]. Since then, there have been many papers on this device, but other techniques, such as the ^{133}Xenon washout method, are also currently used. A recent paper on this topic [67] indicated that the high cutaneous blood flow in lesional psoriatic skin is not due to a maximally passively dilated vascular bed and that the Woronoff ring cannot be ascribed to vasoconstriction.

''NEW DISEASES'' OR NEW ASPECTS OF DISEASES REPORTED IN *THE JOURNAL OF INVESTIGATIVE DERMATOLOGY*

Unless strong errors were made in the method of scanning the JID since 1938, it appears that very few ''new diseases'' or new aspects of diseases have been reported in it. This is most probably due to the fact that ''new diseases'' are most often established initially on clinical and histologic grounds, and are therefore published in clinically oriented journals. The papers that could be included under this heading are as follows: (i) the observation by Sagher *et al* [68] that bone changes may be associated with urticaria pigmentosa, which was considered as ''one of the pure dermatoses'' 1952; (ii) the report by Convit *et al* [69] of Erythema dyschronicum perstans, ''a hitherto undescribed skin disease'' (they described five patients and suggested two names ''erythema chronicum figuratum melanodermicum'' or ''erythema dyschronicum perstans,'' which was finally adopted for being simpler and, as stated the authors, suggested by Sulzberger); and (iii) the report by Soter *et al* [70] on the syndrome urticaria arthralgia and hypocomplementemia, which has been previously put forward by McDuffie (cited in Ref 70). It is interesting to note that up to volume 87, very few (I only found 3) papers on AIDS have been published in the JID.

PATHOPHYSIOLOGY OF SKIN DISEASES

Bacterial and Fungal Infections Besides the studies implying the inoculation *in vivo* in humans, which were dealt with in Section III, a number of significant papers on this topic appeared in the JID.

''Erythrasma is a bacterial infection of the skin,'' reported Sarkany *et al* [71]. The observations satisfied the Koch's postulates, and further, the disease was shown to be dramatically responsive to systemic erythromycin.

Groupe A streptococcal infections are often associated with flares of guttate psoriasis; this led the group of K.D. Wuepper to suspect that certain strains of streptococci might produce a substance which could influence keratinocytes to undergo DNA synthesis and cell division. They purified a factor of 29 000 D from group A type 12 strain NY5 which increased mitosis in the rabbit skin *in vivo* as well as the uptake of ^{3}H thymidine in human lymphocytes [72,73].

Selective bacterial adherence is a first step in the infection of a host cell. Because *staphylococcus aureus* is readily isolated from patients with atopic dermatitis and somewhat less so from those suffering psoriasis, Bibel *et al* [74] considered increased adherence as a possible cause of colonization. They made two important observations: (1) the enhanced binding of staphylococcus aureus on atopic dermatitis epithelial cells as compared to psoriatic and normal cells, and (2) the fact that the degree of adherence was related to the progress of keratinization; the fully keratinized cells carried twice as many staphylococci as the upper level granular cells, which in turn bound twice as many bacteria as the cells of lower layers. We are all waiting for something that would compete with this adherence in atopic dermatitis skin!

Similar studies on adherence to corneocytes were made with six species of *Candida* by Ray *et al* [75]. They found that the species of Candida that possess *in vitro* capability for adherence to epidermal corneocytes and mucosal epithelial cells are the same species (notably *Candida albicans)* associated with colonization and infection. They further observed that fresh serum, possibly through the deposition of complement component onto yeast cell surface, may exert a protective effect by inhibiting Candida adherence to epithelial cells. Ray and Wuepper [76] suggested that accumulation of neutrophilic granulocytes within the epidermis and beneath the stratum corneum in cutaneous candidiasis was due to activation by *Candida alhicans* of the alternative pathway of complement generating chemotatic factors.

There is considerable evidence that *Pityrosporum orbiculare,* an almost ubiquitous skin commensal, is capable of transition to a hyphal phase Pityrosporum furfur (Malassez), the cause of pityriasis versicolor. Because a source of lipid is essential for growth, Catterall *et al* [77] considered that pityrosporum orbiculare must inevitably possess an enzyme capable of utilizing fats. They found that, *in vivo,* Pityrosporum furfur did not show surface lipase activity and concluded that skin surface lipids are not critical for the pathogenesis of pityriasis versicolor. Host susceptibility factors for this disease are still to be clearly identified for preventing relapses and sparing tons of Imidazoles!

The lipolytic activity that liberates free fatty acids from sebaceous triglycerides is derived from *corynehacterium acnes.* This important statement was derived from the observation by Marples *et al* [78] that systemic tetracyclines therapy, which does not affect the other microorganisms (i.e., coagulase negative cocci and Pityrosporum), induces a reduction of free fatty acids.

Observations on Some Commonplace Skin Conditions Many papers addressing the pathophysiology of common benign skin diseases that populate the daily clinic of the practicing dermatologist were published in the JID. They provided interesting observations, many of which should have therapeutical implications, and, at any rate, should give the clinician the possibility of thinking on ''mechanism,'' even when confronted with commonplace skin conditions. The following have been chosen as examples.

''Milia are not retention cysts'' claimed Epstein and Kligman [79], thus correcting the ''fallacy almost universally held'' before their paper was published in 1956. They studied serial sections of several sources, including autotransplants of cutaneous tissues, and put forward the concept that milia should represent a ''simple keratinizing type of benign tumor arising from equipotential cells, anywhere in the cutaneous epithelial system.''

The essential factor in rosacea is recurrent oedema induced by various factors, most notably recurrent flushing [80]. Because it was widely held that coffee provoked flushing in patients with rosacea, Wilkin [80] wondered if its proscription and its substitution by ''decaffeinated coffee'' as ''often suggested in major textbooks'' were justified. He measured the malar thermal circulation index and malar skin temperature and found *hot* coffee, but not cold coffee nor caffeine, to be responsible for flushing in rosacea patients. ''The probable mechanism by which ingested heat leads to the flushing reaction is based on a counter-current heat exchange at the level of the internal jugular vein and common carotid artery, and subsequently a central thermoregulatory reflex'' he concluded. A nice piece of clinical research!

''Although callosities of the plantar skin are common and often disabling, little is known of their pathology or the reasons for their persistance'' stated Marks *et al* [81]. They found increased thymidine autoradiographic labeling indexes in callosities as well as abnormalities in corneocytes, such as decreased density and apparent reduced shedding (as shown by the dansyl chloride test). So far these studies have not provided informations on how to prevent callosities and how to better treat them. No doubt, the Welsh investigators will tell us more in the future!

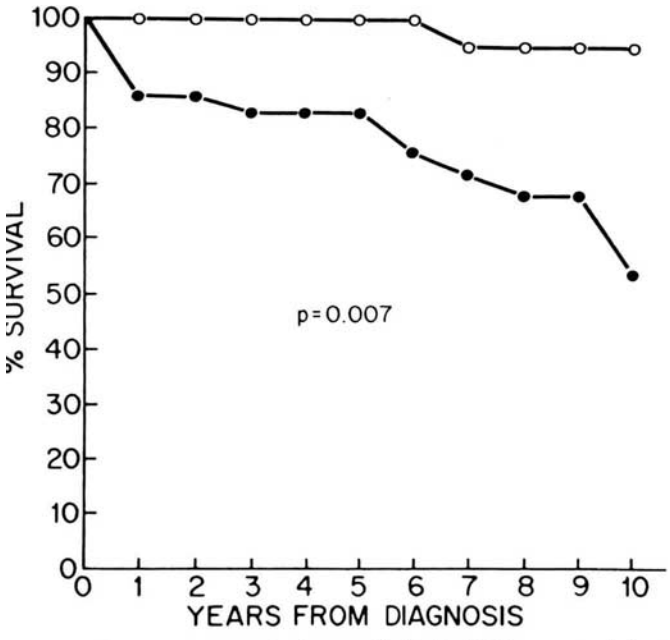
Is circumscribed sebaceous gland hyperplasia often found in the face of adults and aged because of increased proliferation of sebocytes? The answer is no, as shown by a study by Lunderschmidt and Plewig [82]. They found slowed down transit and turnover time as well as decreased labeling indices, as compared with the uninvolved sebaceous glands of the same ederly subjects. Should we consider another denomination for that condition, such as ''retentional sebaceous hypertrophy''?

Skin limited amyloidoses is another commonplace situation in practice. Hashimoto has been instrumental in bringing the concept that, with the exception of some nodular amyloidosis, the amyloid substance is ''keratinoid amyloid.'' In order to outline how editorials published in the JID (a painful task for editors and authors!) are useful, I urge you to read or reread Hashimoto's editorial in 1984 on cutaneous amyloidoses [83]. It depicts how electron microscopy, immunologic, and biochemical methods allowed the identification of the source of amyloid in skin limited amyloidoses, i.e., the apoptotic keratinocyte.

Maturing Clinical Research in ''Major'' Dermatoses Many ''major'' dermatoses fall into one of the sections covered by the other associate editors, such as genetics, immunology, cell biology, etc. They also fully pertain to clinical research because papers published in the JID often drastically modified understanding and therapy of several major diseases, thus having direct clinical impact. As examples of this category, the report by Schlitz and Michel [84] on the induction of acantholysis by the IgG fraction of pemphigus serum in human skin *in vitro* and Bauer *et al* [85] on the role of skin collagenase in dystrophic epidermolysis bullosa should be included. Atopic dermatitis has not been covered in this review. This probably reflects the fear and lazyness of the author when looking at the huge number of papers published in the JID since 1938 on this condition. ''We are still waiting for the key paper, paving the way for significant progress in pathophysiology and therapy. It seems we are still descriptive, even when sophisticated biochemical and immunologic methods are used. To stay on descriptive morphology, the paper by Mihm *et al* [86] has become a classic, even if the authors state in the introduction ''the purpose of this presentation is to provide a brief description of normal cutaneous histology as observed in 1 um-thick Epon embedded sections and to describe the alterations which characterize atopic eczema.''

An interesting example of maturing clinical research is to look at a succession of JID papers dealing with congenital ichthyoses. A histologic study by Wells and Kerr [87] showed the distinct patterns of autosomal dominant ichthyosis as compared to X linked lchthyosis. Frost *et al* [88] reported the same year that excessive proliferation, as shown by autoradiography, is a feature of lamellar ichthyosis and ''epidermolytic hyperkeratosis,'' whereas it is not found in ichthyosis vulgaris. By grafting the skin of lamellar ichthyosis onto nude mice, Briggaman and Wheeler [89] suggested that the defective gene in this disease acts directly on the epidermis. Biochemical techniques allowed Sybert *et al* [90] to observe that profilaggrin and filaggrin are reduced in the epidermis of ichthyosis vulgaris, in which keratohyahne granules are absent or reduced. We shall learn more on ichthyoses by reading the JID in the near future (Fig 4).

I would like to close this section by referring to the last paper by a gentleman of modern Dermatology, Dr. J.N. Gillian, who died while the final draft of his manuscript was being prepared. This study [91], an example of ''clinical research'' in Dermatology, is on the prognostic significance of the lupus band test in uninvolved skin of patients with lupus erythematosous. It is a 10-year longitudinal study



Comparative survival rates of initially LBT-negative (O) and LBT-positive (●) SLE patients.

Figure 4. The best demonstration of the usefulness of the lupus band test in identifying a subset of SLE patients with ''more aggressive renal disease and decreased long-term survival.'' (From Davis BM, Gilliam JN: J Invest Dermatol 83:242–247, 1984)

in 51 patients. It indicates that the test does have ''predictive value in that it identifies a subset of SLE patients with more aggressive renal disease and significantly decreased long-term survival.''

RETINOIDS IN THE JID

About sixty papers have been published in the JID on vitamin A and retinoids; only three are within the 200 top cited papers. As one would expect, more than 50% were published after 1980, whereas three appeared in the 1940s, eight in the 1950s, seven in the 1960s, and eight in the 1970s. It is beyond the scope of this review to comment on all these papers. They are listed in Table IV under four headings.

Reports on therapeutic use of retinoids have been very few. Although the observation was made in animals, the fact that trichophyton verrucosum infection might be cured by systemic administration of vitamin A (Table IV) is interesting. The author of the present review is not aware of a trial of topical retinoids in human dermatophytosis. Such a use of retinoids might increase their market value, although not to the level of their use for skin aging.

The number of *in vitro* studies was not as high as expected (Table IV) and the observations made herein are sometimes difficult to integrate into the *in vivo* situation. Many important contributions on the metabolism of retinoids *in vivo* appeared in the JID. Although none is in the 200 top cited papers (possibly because they are recent), some will remain key references, notably the series of papers from the Uppsala group. The bulk of papers on retinoids dealt with *in vivo* studies on the mode of action in the skin. Many of these have been

Table IV. Papers on Vitamin A and Retinoids in the JID (Vol 1-87)[a]

Use for therapy	
Systemic acqueous vitamin A for acne vulgaris	1949, 12:221
	1950, 14:283
Cure of trichophyton verrucosum infection by systemic vitamin A in cattle	1964, 42:173
Etretinate enhances PUVA	1978, 70:178[b]
In vitro studies	
RA exert on mitogenic activity on post embryonal epidermal cells	1973, 63:450
Vitamin A affects growth and differentiation in epidermal outgrowth	1975, 64:19
Effects of RA on embryonic chick skin	1977, 69:463
Effects of several retinoids on embryonic chick skin	1979, 72:11
Effects of retinol in morphogenesis of mouse vibrissae	1978, 71:286
RA causes premature desquamation in keratinocytes cultures	1982, 79:253
RA modulates fibroblast collagenase activity	1983, 81:162
RA increases expression of pemphigus antigen and cytoplasmic expression of BP antigen	1984, 82:329
Structure activity of retinoids in chick embryo morphogenesis	1984, 83:105
Etretinate and RA modulate beta adremagic arenylate cyclase response	1985, 85:324
Retinol modulates Langerhans cell markers and IL_1 production	1985, 85:501
In vitro metabolism of isotretinoin by preputial glands	1985, 85:465
Studies on metabolism (in vivo)	
Sex difference in vitamin A metabolism	1950, 15:409
Liver vitamin A in Darier's disease	1954, 23:71
Percutaneous absorption of vitamin A	1958, 30:315
Percutaneous and oral absorption of vitamin A	1958, 31:575 and 577
Carotinoids in sebum after oral intake	1958, 31:599
Topical use of tritiated retinoic acid	1971, 55:249
Topical use of tritiated retinoic acid	1971, 57:323
Vitamin A metabolism in human skin	1982, 79:89 and 94
Milk intake increases etretinate absorption	1984, 82:636
UV irradiation reduces retinol in epidermis	1984, 83:401
Pharmacokinetics of topically applied retinoids	1985, 84:184
Biosynthesis of vitamin A_2 from retinol	1985, 85:498

Table IV. Continued

Serum and skin concentrations of isotretinoin and retinol during oral therapy for acne	1986, 86:384
In vivo studies on the mode of action	
Mode of action of vitamin A (an historical forum)	1953, 21:421
Response of mouse skin to topical vitamin A	1956, 26:69
Response of mouse skin to topical vitamin A	1958, 31:313[b]
Biometric analysis of the effects of oral vitamin A on human epidermis	1961, 37:459
Vitamin A deficiency reduces epidermal mitosis	1961, 37:469[b]
Topical RA affects hyperkeratinization	1967, 49:165
	1970, 54:126
Topical RA increases mitotic indexes	1973, 59:228
Topical RA increases PGE, cAMP and cGMP	1976, 67:231
Ultrastructural study of the effect of topical RA	1979, 73:203
Isotretinoin induced inhibition of Hamster flank organ is not an anti androgen effect	1980, 74:392
Etretinate, unlike isotretinoin does not affect Hamster flank organ	1981, 76:68
Inhibition of UV induced carcinogenesis by RA	1981, 76:178
Oral administration of etretinate increases epidermal cell proliferation in hairless mice	1981, 77:287
Topical RA increases epidermal transglutaminase	1982, 79:189
Freeze fracture study of the effect of etretinate on psoriatic epidermis	1983, 80:174
Etretinate reduces urinary polyamines in psoriatic patients	1983, 80:181
Effect of etretinate on Langerhans cells	1983, 81:10
Etretinate reduces neutrophil chemotaxis	1983, 81:418
Cellular retinoid binding proteins in epidermis and sebaceous glands	1984, 82:79
Topical retinoids effect on rhino mouse utricules	1984, 82:632
Topical and systemic effect on rhino mouse utricules	1984, 83:110
Topical RA inhibits S91 melanoma growth	1985, 85:89
Cellular RA binding protein in chick embryos skin	1985, 85:279
Cellular RA binding protein in normal human skin	1985, 85:460
Cellular RA binding protein increased in psoriatic plaques	1986, 86:42
Isotretinoin therapy changes cutaneous bacterial flora	1986, 86:390
Systemic etretin increases cellular RA binding protein in human epidermis	1986, 76:122
Topical RA effect on dermal collagen and glycosaminoglycans	1986, 87:663

[a]Although most of the papers are listed, it may be that some had escaped the method of collecting the data.
[b]Indicates the paper is in the 200 top cited papers.

made in human because systemic synthetic retinoids were used as therapeutic agents. A historical ''forum'' followed the paper published by Flesh in 1953 [92]. It is interesting that the last sentence of the discussion, in which many prominent dermatologists of that time participated, says ''A strict distinction between the physiological and the pharmacological effects of vitamin A may be impossible.'' Table IV lists most of the studies published since in the JID. Despite the important message given in many of these reports, we still have no answer to the question raised by Flesh and do not know how retinoids work in human skin. It is hoped that the key paper on this issue will soon appear in this Journal.

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